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EXAMINER	
WILSON, MICHAEL C	
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1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,653	ROGLER ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *17-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 39-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-16 and 39-47 in the reply filed on 9-25-07 is acknowledged.

Claims 17-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9-25-07.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 39-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 46 are indefinite because the phrase "expression of said uPA gene resulting in liver degeneration" does not clearly set forth expression of said uPA occurs and results in liver degeneration.

Claim 7 is indefinite because "to generate F1 uPA hemizygous, RAG-2 hemizygous sibling mice" does not clearly set forth the F1 mice are hemizygous for the uPA gene and hemizygous for the disrupted RAG-2 gene. The term "sibling" appears to be unnecessary in the phrase.

Claim 7 is indefinite because "a RAG2 homozygous mouse" does not clearly set forth the mouse is homozygous for the disrupted RAG2 gene.

Claim 7 is indefinite because "to generate a uPA hemizygous or homozygous, RAG2 homozygous (uPA/RAG2) F2 mouse" does not clearly set forth the F2 mouse is hemizygous or homozygous for the uPA gene and homozygous for the disrupted RAG2 gene. Use of "(uPA/RAG2)" does not appear to be necessary because it is not used later in the claims.

The term repopulation in claim 4 lacks antecedent basis.

The phrase "said transplantation" in claim 10 lacks antecedent basis.

The phrase "said repopulation" claim 11 lacks antecedent basis.

Claim 39 is indefinite because it does not clearly set forth the chimeric mouse has a genome comprising a uPA gene as in claim 1. The format of claim 1, step a, should be used in claim 39, step a, with the changes made to the "expression" phrase cited above.

Claim 41 is unclear because it cannot be determined when human hepatocytes reconstitute "10% of the degenerated liver" as claimed. It is unclear if the human hepatocytes must be 10% of the total number of cells in the degenerated liver before or after transplanting.

The phrase "said repopulation" in claim 44 lacks antecedent basis

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-7 and 9-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Petersen (PNAS, January 1998, Vol. 95, pg 310-315).

Petersen taught a chimeric mouse expressing uPA that had a RAG-2 gene knockout; the chimeric mouse was made by crossing a uPA mouse with a RAG-2 knockout mouse (pg 311, methods; Generation of Tolerant uPA/RAG-2 mice). The mouse was immunotolerant and lacked functional T and B cells as claimed because RAG-2 activation caused a lack of T and B cells (abstract). The chimeric uPA/RAG-2 mouse had a degenerated liver and woodchuck hepatocytes (see results first paragraph). Petersen infected the woodchuck hepatocytes with woodchuck hepatitis virus (WHV) prior to (pg 312 first paragraph; pg 314 first paragraph) or after transplantation (pg 313; Infection of woodchuck hepatocytes in uPNRAG-2 mice). Petersen tested the effects of interferon α and dexamethasone for antiviral and

anticancer (page 313, and discussion: whole text) activity in the same chimeric mice, as compared to controls, that were infected with woodchuck hepatitis virus prior to and/or after transplantation of woodchuck hepatocytes. Petersen taught the formation of hepatocellular carcinomas from transplanted premalignant tissue as well as the presence of unique viral integration sites in a chimeric mouse as compared to a control donor mouse. Without evidence to the contrary, the uPA is inherently "secreted" as claimed (claims 2, 12, 42) because it is functionally expressed as evidenced by the phenotypic changes in the transgenic mice. Claims 6 and 14 are included because WHV is inherently part of the Hepatitis B family.

Claims 1-6, 8-14, 16, 39 and 42-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Kay (US Patent 5,980,886).

Kay taught mice containing a uPA transgene expressing uPA specifically in the liver had a functional liver deficit (col. 2, lines 52-55). The uPA gene has been used to impair native liver function and stimulate repopulation of liver with non-native cells (col. 3, lines 3-6).

> "In one embodiment the non-human animals of the present invention contain a transgene which encodes a modified non-secreted uPA as described herein, e.g., uPA having a modified C-terminus containing KDEL, uPA having the signal peptide on the N-terminus substituted by the RR retention signal and transmembrane region of the type II transmembrane proteins (Schutze et al., EMBO J. 13: 1696-1705 (1994); Gorlich et al., Nature 357: 47-52 (1992), or a combination of both C-terminal and N-terminal modifications designed to inhibit secretion of the uPA molecule without substantially adversely affecting hepatotoxic activity. Expression of the modified uPA can be under the control of an inducible or constitutive promoter, e.g., the cytochrome P450 promoter of Jones et al., Nucl. Acids Res. Simultaneous with or subsequent to expression of the secretion impaired uPA transgene, non-native (e.g., human) hepatocytes are implanted in the transgenic mammal, e.g., a nude or immunodeficient SCID mice, to reconstitute the mammal's liver with a large proportion of non-native (e.g.,

human) hepatocytes. The mammal is then used as a model for ex vivo hepatic gene transfer, or it can serve as a model, for example, of human hepatitis C infection and its treatment, e.g., with ribozymes against hepatitis C viral RNA." (col. 7, line 64, through col. 8, line 18).

"Ribozyme producing cell lines are compared for the production of HCV RNA. The sequences encoding the selected ribozymes are placed into adenoviral vectors and used to transduce the hepatocytes of the animal of interest, e.g., mice in which the liver has been ablated with the urokinase gene as described herein and reconstituted with human hepatocytes. For example, SCID mice that have livers reconstituted with human hepatocytes are infused with hepatitis C particles, or human HCV-infected hepatocytes are used in the reconstitution process. The liver and serum of the animals are monitored for production of virus by quantitative RT-PCR assays." (col. 8, line 55-65)

"The invention also provides non-human mammals with functioning non-native liver, e.g., human, or native liver which expresses a desired gene product. The animals can be used as models for evaluating a wide variety of disease processes and treatments. For example, the animal models can be used to as models of pathogenesis for infections, e.g., viral infections such as human hepatitis viruses A, B and C, CMV, or the like, or to determine the effectiveness and safety of treatments or vaccines for such infections. The animals also find use for evaluating the treatment and prevention of genetic disorders..." (col. 7, lines 51-61)

The transgenic uPA mouse with human hepatocytes, "e.g. a nude or immunodeficient SCID mice" infused with HCV or HCV-infected hepatocytes described by Kay is equivalent to the chimeric mouse of claim 1.

Claim 39 is included because the patent office does not have the ability to test the viability of human hepatocytes taught by Kay; therefore, without evidence to the contrary, the human hepatocytes transplanted by Kay would have at least 80% viability.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5, 6, 8-10, 12-14, 16, 39-43, 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhim (PNAS, May 1995, Vol. 92, pg 4942-4946) in view of Vierling (Hepatology, Oct. 1996, Vol. 24, No. 4, Pt. 2, pg 218A).

Rhim taught crossing a Swiss nude mouse lacking T cells (but not B cells) with an Alb-uPA transgenic mouse and obtaining a chimeric mouse lacking T cells (but not B cells) that expressed uPA resulting in liver degeneration (pg 4942, col. 2, "Generation of immunotolerant Alb-uPA transgenic mice). Rat hepatocytes were injected into the

parenchyma of the livers of 10-15 day old immunotolerant transgenic mice (pg 4942, col. 2, last full paragraph). Rhim also taught reconstituting the mouse liver with human hepatocytes (pg 4946, col. 1, last full paragraph). Without evidence to the contrary, the uPA is inherently "secreted" as claimed (claims 2, 12, 42) because it is functionally expressed as evidenced by the phenotypic changes in the transgenic mice. Rhim did not teach the chimeric mouse lacked B cells or that the rat or human hepatocytes used for transplantation were infected with hepatitis virus.

However, Vierling taught reconstituting SCID mouse liver with human hepatocytes infected with human HCV before transplantation (see entire abstract). SCID mice inherently lack T and B cells.

Thus, it would have been obvious to those of ordinary skill in the art at the time of filing to obtain a chimeric mouse that was immunotolerant comprising the uPA gene, wherein expression of the uPA gene caused liver degeneration, then transplant rat or human hepatocytes into the parenchyma of the liver as described by Rhim, wherein the immunotolerant mouse was a SCID mouse as described by Vierling. Those of ordinary skill in the art at the time of filing would have been motivated to replace the Swiss nude mouse of Rhim with the SCID mouse of Vierling to reduce the ability of the mouse's immune response to reject the xenotransplanted tissue.

It also would have been obvious to those of ordinary skill in the art at the time of filing to obtain a chimeric mouse that was immunotolerant comprising the uPA gene, wherein expression of the uPA gene caused liver degeneration then transplant human hepatocytes into the parenchyma of the liver as described by Rhim, wherein the human

hepatocytes were infected with human HCV as described by Vierling. Those of ordinary skill in the art at the time of filing would have been motivated to infect the human hepatocytes with human HCV prior to transplantation to model human HCV infection.

Claim 39 is included because the patent office does not have the ability to test the viability of the hepatocytes transplanted by Vierling; therefore, without evidence to the contrary, the human hepatocytes transplanted by Vierling had at least 80% viability. It is noted that the viability of rat hepatocytes transplanted by Rhim was 50-90%. Since some of the rat hepatocytes transplanted by Rhim were at least 80% viable as claimed, it is reasonable to conclude that some of the human hepatocytes transplanted by Vierling were at least 90% viable as claimed too.

Claim 41 is included because the patent office does not have the ability to test the percentage of human hepatocytes in the reconstitute mouse liver; therefore, without evidence to the contrary, the human hepatocytes infected with human HCV would comprise at least 10% of the transgenic mouse liver.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-16, 39 and 42-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay (US Patent 5,980,886) in view of Alt (US Patent 5,583278).

Kay taught mice containing a uPA transgene expressing uPA specifically in the liver had a functional liver deficit (col. 2, lines 52-55). The uPA gene has been used to

impair native liver function and stimulate repopulation of liver with non-native cells (col. 3, lines 3-6).

"In one embodiment the non-human animals of the present invention contain a transgene which encodes a modified non-secreted uPA as described herein, e.g., uPA having a modified C-terminus containing KDEL, uPA having the signal peptide on the N-terminus substituted by the RR retention signal and transmembrane region of the type II transmembrane proteins (Schutze et al., EMBO J. 13: 1696-1705 (1994); Gorlich et al., Nature 357: 47-52 (1992), or a combination of both C-terminal and N-terminal modifications designed to inhibit secretion of the uPA molecule without substantially adversely affecting hepatotoxic activity. Expression of the modified uPA can be under the control of an inducible or constitutive promoter, e.g., the cytochrome P450 promoter of Jones et al., Nucl. Acids Res. Simultaneous with or subsequent to expression of the secretion impaired uPA transgene, non-native (e.g., human) hepatocytes are implanted in the transgenic mammal, e.g., a nude or immunodeficient SCID mice, to reconstitute the mammal's liver with a large proportion of non-native (e.g., human) hepatocytes. The mammal is then used as a model for ex vivo hepatic gene transfer, or it can serve as a model, for example, of human hepatitis C infection and its treatment, e.g., with ribozymes against hepatitis C viral RNA." (col. 7, line 64, through col. 8, line 18).

"Ribozyme producing cell lines are compared for the production of HCV RNA. The sequences encoding the selected ribozymes are placed into adenoviral vectors and used to transduce the hepatocytes of the animal of interest, e.g., mice in which the liver has been ablated with the urokinase gene as described herein and reconstituted with human hepatocytes. For example, SCID mice that have livers reconstituted with human hepatocytes are infused with hepatitis C particles, or human HCV-infected hepatocytes are used in the reconstitution process. The liver and serum of the animals are monitored for production of virus by quantitative RT-PCR assays." (col. 8, line 55-65)

"The invention also provides non-human mammals with functioning non-native liver, e.g., human, or native liver which expresses a desired gene product. The animals can be used as models for evaluating a wide variety of disease processes and treatments. For example, the animal models can be used to as models of pathogenesis for infections, e.g., viral infections such as human hepatitis viruses A, B and C, CMV, or the like, or to determine the effectiveness and safety of treatments or vaccines for such infections. The animals also find use for evaluating the treatment and prevention of genetic disorders..." (col. 7, lines 51-61)

The transgenic uPA mouse with human hepatocytes, "e.g. a nude or immunodeficient SCID mice" infused with HCV or HCV-infected hapatocytes described by Kay is equivalent to the chimeric mouse of claim 1.

Claim 39 is included because the patent office does not have the ability to test the viability of human hepatocytes taught by Kay; therefore, without evidence to the contrary, the human hepatocytes transplanted by Kay would have at least 80% viability.

Kay did not teach crossing a uPA transgenic mouse with a RAG-2 knockout mouse to generate uPA/RAG-2 mice as claimed.

However, Alt taught mice with a homozygous disruption of the RAG-2 gene had an improved SCID phenotype (column 2).

Thus, it would have been obvious to those of ordinary skill in the art at the time of filing to obtain a chimeric SCID mouse comprising the uPA gene, wherein expression of the uPA gene caused liver degeneration, then infuse HCV into human hepatocytes transplanted into the mice or transplant human HCV-infected hepatocytes human into the parenchyma of the liver as described by Kay, wherein the SCID mouse was a RAG-2 knockout as claimed. In particular, it would have been obvious to those of ordinary skill in the art at the time the claimed invention was made to modify the teachings of Kay by breeding a RAG-2 knockout mouse with a uPA homozygous transgenic mouse to create a RAG-2/uPA homozygous mouse that could be the recipient of transplanted human hepatocytes infected with HCV. Those of ordinary skill would have been motivated to use the RAG-2 homozygous knockout mouse of Alt instead of the traditional SCID mouse described by Kay because Alt taught that traditional SCID mice

had a leaky phenotype that could still result in the production of B and T lymphocytes because of VDJ rearrangement. Alt taught RAG-2 deficient mice had an improved SCID phenotype that was not leaky.

Those of ordinary skill in the art would have readily recognized that the crossing in claim 7 was the only way the uPA transgene could be put onto the Rag-2 knockout background of Alt, and would inherently result in a +/- uPA and -/- RAG-2 F2 mouse or a +/+ uPA and -/- RAG-2 F2 mouse. In particular, those of ordinary skill in the art would have readily recognized that the F2 mouse had to be homozygous for the RAG-2 knockout to be immunotolerant.

Claim 39 is included because the patent office does not have the ability to test the viability of human hepatocytes taught by Kay; therefore, without evidence to the contrary, the human hepatocytes transplanted by Kay would have at least 80% viability.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-6, 8-14, 16, 39, 42-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay (US Patent Office 5,980,886) as supported by Vierling (Hepatology, Oct. 1996, Vol. 24, No. 4, Pt. 2, pg 218A).

Kay taught mice containing a uPA transgene expressing uPA specifically in the liver had a functional liver deficit (col. 2, lines 52-55). The uPA gene has been used to impair native liver function and stimulate repopulation of liver with non-native cells (col. 3, lines 3-6).

"In one embodiment the non-human animals of the present invention contain a transgene which encodes a modified non-secreted uPA as described herein, e.g., uPA having a modified C-terminus containing KDEL, uPA having the signal peptide on the N-terminus substituted by the RR retention signal and transmembrane region of the type II transmembrane proteins (Schutze et al., EMBO J. 13: 1696-1705 (1994); Gorlich et al., Nature 357: 47-52 (1992), or a combination of both C-terminal and N-terminal modifications designed to inhibit secretion of the uPA molecule without substantially adversely affecting hepatotoxic activity. Expression of the modified uPA can be under the control of an inducible or constitutive promoter, e.g., the cytochrome P450 promoter of Jones et al., Nucl. Acids Res. Simultaneous with or subsequent to expression of the secretion impaired uPA transgene, non-native (e.g., human) hepatocytes are implanted in the transgenic mammal, e.g., a nude or immunodeficient SCID mice, to reconstitute the mammal's liver with a large proportion of non-native (e.g., human) hepatocytes. The mammal is then used as a model for ex vivo hepatic gene transfer, or it can serve as a model, for example, of human hepatitis C infection and its treatment, e.g., with ribozymes against hepatitis C viral RNA." (col. 7, line 64, through col. 8, line 18).

"Ribozyme producing cell lines are compared for the production of HCV RNA. The sequences encoding the selected ribozymes are placed into adenoviral vectors and used to transduce the hepatocytes of the animal of interest, e.g., mice in which the liver has been ablated with the urokinase gene as described herein and reconstituted with human hepatocytes. For example, SCID mice that have livers reconstituted with human hepatocytes are infused with hepatitis C particles, or human HCV-infected hepatocytes are used in the reconstitution process. The liver and serum of the animals are monitored for production of virus by quantitative RT-PCR assays." (col. 8, line 55-65)

"The invention also provides non-human mammals with functioning non-native liver, e.g., human, or native liver which expresses a desired gene product. The animals can be used as models for evaluating a wide variety of disease processes and treatments. For example, the animal models can be used to as models of pathogenesis for infections, e.g., viral infections such as human hepatitis viruses A, B and C, CMV, or the like, or to determine the effectiveness and safety of treatments or vaccines for such infections. The animals also find use for evaluating the treatment and prevention of genetic disorders..." (col. 7, lines 51-61)

The transgenic uPA mouse with human hepatocytes, "e.g. a nude or immunodeficient SCID mice" infused with HCV or HCV-infected hapatocytes described by Kay is equivalent to the chimeric mouse of claim 1.

Claim 39 is included because the patent office does not have the ability to test the viability of human hepatocytes taught by Kay; therefore, without evidence to the contrary, the human hepatocytes transplanted by Kay would have at least 80% viability.

Vierling taught reconstituting SCID mouse liver with human hepatocytes infected with human HCV before transplantation (see entire abstract). SCID mice inherently lack T and B cells.

Thus, it would have been obvious to those of ordinary skill in the art at the time of filing to obtain an immunotolerant SCID mouse comprising the uPA gene, wherein expression of the uPA gene caused liver degeneration and transplant human HCV-infected hepatocytes human into the parenchyma of the liver of the mouse as described by Kay, and to infect the immunotolerant mouse with human HCV-infected haptocytes as described by Vierling. Those of ordinary skill in the art would have recognized that reconstituting SCID mouse liver with human hepatocytes infected with human HCV before transplantation as taught by Kay was known in the art at the time of filing as described by Vierling. Those of ordinary skill in the art at the time the claimed invention was made to use the technique described by Vierling in the method described by Kay because Vierling taught viable human hepatocytes persisted for at least 5 days.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-6, 8-14, 16 and 39-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhim (PNAS, May 1995, Vol. 92, pg 4942-4946) in view of Vierling

(Hepatology, Oct. 1996, Vol. 24, No. 4, Pt. 2, pg 218A) as applied to claims 1-3, 5, 6, 8-10, 12-14, 16, 39-43, 45-47 above and further in view of Kay (US Patent 5,980,886).

The combined teachings of Rhim and Vierling taught crossing a SCID mouse (lacking T cells and B cells) with an Alb-uPA transgenic mouse and obtaining a chimeric mouse (lacking T cells and B cells) that expressed uPA resulting in liver degeneration, and injecting HCV infected human hepatocytes into the parenchyma of the livers of SCID transgenic mice when they were 10-15 day old (see 103 rejection above). The combined teachings of Rhim and Vierling did not teach administering HCV following repopulating the liver of the SCID transgenic mice as claimed.

However, Kay taught:

> SCID mice that have livers reconstituted with human hepatocytes are infused with hepatitis C particles, or human HCV-infected hepatocytes are used in the reconstitution process. The liver and serum of the animals are monitored for production of virus by quantitative RT-PCR assays." (col. 8, line 55-65)

Kay also confirms the desire to make immunotolerant SCID mice containing a uPA transgene expressing uPA specifically in the liver for injecting human hepatocytes and human HCV.

> "In one embodiment the non-human animals of the present invention contain a transgene which encodes a modified non-secreted uPA as described herein, e.g., uPA having a modified C-terminus containing KDEL, uPA having the signal peptide on the N-terminus substituted by the RR retention signal and transmembrane region of the type II transmembrane proteins (Schutze et al., EMBO J. 13: 1696-1705 (1994); Gorlich et al., Nature 357: 47-52 (1992), or a combination of both C-terminal and N-terminal modifications designed to inhibit secretion of the uPA molecule without substantially adversely affecting hepatotoxic activity. Expression of the modified uPA can be under the control of an inducible or constitutive promoter, e.g., the cytochrome P450 promoter of Jones et al., Nucl. Acids Res. Simultaneous with or subsequent to expression of the secretion impaired uPA transgene, non-native (e.g., human) hepatocytes are

implanted in the transgenic mammal, e.g., a nude or immunodeficient SCID mice, to reconstitute the mammal's liver with a large proportion of non-native (e.g., human) hepatocytes. The mammal is then used as a model for ex vivo hepatic gene transfer, or it can serve as a model, for example, of human hepatitis C infection and its treatment, e.g., with ribozymes against hepatitis C viral RNA." (col. 7, line 64, through col. 8, line 18).

"Ribozyme producing cell lines are compared for the production of HCV RNA. The sequences encoding the selected ribozymes are placed into adenoviral vectors and used to transduce the hepatocytes of the animal of interest, e.g., mice in which the liver has been ablated with the urokinase gene as described herein and reconstituted with human hepatocytes. For example, SCID mice that have livers reconstituted with human hepatocytes are infused with hepatitis C particles, or human HCV-infected hepatocytes are used in the reconstitution process. The liver and serum of the animals are monitored for production of virus by quantitative RT-PCR assays." (col. 8, line 55-65)

"The invention also provides non-human mammals with functioning non-native liver, e.g., human, or native liver which expresses a desired gene product. The animals can be used as models for evaluating a wide variety of disease processes and treatments. For example, the animal models can be used to as models of pathogenesis for infections, e.g., viral infections such as human hepatitis viruses A, B and C, CMV, or the like, or to determine the effectiveness and safety of treatments or vaccines for such infections. The animals also find use for evaluating the treatment and prevention of genetic disorders..." (col. 7, lines 51-61)

Thus, it would have been obvious to those of ordinary skill in the art at the time of filing to obtain a chimeric SCID mouse comprising the uPA gene, then transplant human hepatocytes into the parenchyma of the liver as described by the combined teachings of Rhim and Vierling, wherein the human hepatocytes were infected with HCV following transplantation as taught by Kay ("reconstituted with human hepatocytes are infused with hepatitis C particles" (col. 8, lines 55-65). Those of ordinary skill in the art at the time of filing would have been motivated to infect the human hepatocytes with HCV after transplantation of the human hepatocytes as suggested by Kay to more closely model human infection with HCV.

Claim 39 is included because the patent office does not have the ability to test the viability of the hepatocytes transplanted by Vierling; therefore, without evidence to the contrary, the human hepatocytes transplanted by Vierling had at least 80% viability. It is noted that the viability of rat hepatocytes transplanted by Rhim was 50-90%. Since some of the rat hepatocytes transplanted by Rhim were at least 80% viable as claimed, it is reasonable to conclude that some of the human hepatocytes transplanted by Vierling were at least 90% viable as claimed too.

Claim 41 is included because the patent office does not have the ability to test the percentage of human hepatocytes in the reconstitute mouse liver; therefore, without evidence to the contrary, the human hepatocytes infected with human HCV would comprise at least 10% of the transgenic mouse liver.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-16 and 39-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-46 of U.S. Patent No. 6864402. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious in view of the disclosure of '402. The claims in the instant application could have been pursued the '402 Patent.

The term "secreted" in claims 2, 12, and 42 of this application was found to be implicit in the specification in application 09/344189, now US Patent 6,864,402. The term appeared in claims filed on 5-23-02. The issue was raised by the examiner in the office action on 8-7-02. Applicants provided explanation why the term was implicit in the response filed Nov. 11, 2002 in the paragraph bridging pg 6-7. The rejection was dropped in the office action on 3-26-03.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now

contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Patent Examiner